# Transient response to nivolumab and relapse after infliximab in a patient with primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

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## References

1 Vossen A, van der Zee HH, Prens EP. Hidradenitis suppurativa: a systematic review integrating inflammatory pathways into a cohesive pathogenic model. *Front Immunol* 2018; **9**:2965.
2 Frew JW, Navrazhina K, Byrd AS *et al.* Defining lesional, perilesional and unaffected skin in hidradenitis suppurativa: proposed recommendations for clinical trials and translational research studies. *Br J Dermatol* 2019; **181**:1339–41.
3 Orro K, Smirnova O, Arshavskaja J *et al.* Development of TAP, a non-invasive test for qualitative and quantitative measurements of biomarkers from the skin surface. *Biomark Res* 2014; **2**:20.
4 Kanni T, Tzanetakou V, Savva A *et al.* Compartmentalized cytokine responses in hidradenitis suppurativa. *PLoS One* 2015; **10**:e0130522.
5 Van der Zee HH, Laman JD, de Ruiter L *et al.* Adalimumab (antitumour necrosis factor-α) treatment of hidradenitis suppurativa ameliorates skin inflammation: an *in situ* and *ex vivo* study. *Br J Dermatol* 2012; **166**:298–305.
6 Hotz C, Boniotto M, Guguin A *et al.* Intrinsic defect in keratinocyte function leads to inflammation in hidradenitis suppurativa. *J Invest Dermatol* 2016; **136**:1768–80.
7 Sørensen OE, Thapa DR, Rosenthal A *et al.* Differential regulation of β-defensin expression in human skin by microbial stimuli. *J Immunol* 2005; **174**:4870–9.

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## Transient response to nivolumab and relapse after infliximab in a patient with primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

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Dear Editor, Primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma ($CD8^+$ AECTCL) is a very rare subtype of cutaneous T-cell lymphoma. The frequency is less than 1% of all primary cutaneous lymphomas and prognosis is poor, with a 5-year disease-specific survival rate of 31%.[1] Because of the rarity of this entity, there are no evidence-based treatment options.

We report the case of a 70-year-old female patient who presented with a red plaque with central ulceration on the left shin rapidly developing in 2 weeks. Skin biopsy revealed atypical lymphoid cells in the epidermis and dermis with atypical mitoses (Figure 1a). Immunohistochemical stains showed reactivity with CD3, CD8 (Figure 1b), TIA-1 and programmed cell death 1 ligand 1, with weak reactivity for programmed cell death protein 1 (PD-1) expression. CD2, CD4, CD20, CD30 and CD56 were negative. Cranial magnetic resonance imaging (MRI) and computed tomography (CT) scan of neck, thorax and abdomen showed no evidence of metastases. Bone marrow biopsy revealed no infiltration with lymphoma cells, and blood count was normal. Primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma was diagnosed.

Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) every 21 days was started. After six cycles of chemotherapy the plaque was clearly regressive, and consolidating radiotherapy of the left lower leg was started. Still on radiotherapy, the patient developed disseminated, well demarcated erythematous patches and plaques, many with necrotic ulcerations, involving all extremities and trunk (Figure 1c), and ulceration on the hard palate. Cranial MRI, CT scan and fluorescence-activated cell sorting analysis ruled out extracutaneous manifestation. Photochemotherapy with psoralen plus ultraviolet A and treatment with topical corticosteroids class IV were initiated without significant improvement. Due to progression, therapy was changed to an anti-PD-1 antibody. After five infusions of nivolumab (2 mg $kg^{-1}$) the patient experienced near complete remission of all lesions (Figure 1d). Only a singular new erythematous plaque with no ulceration appeared on the trunk during treatment. An additional skin biopsy was performed, which showed similar findings to the initial diagnostic specimen. After seven infusions of nivolumab she developed autoimmune diarrhoea grade 2 (Common Terminology Criteria for Adverse Events). Therapy was paused and treatment with prednisolone at 1 mg $kg^{-1}$ orally was started and slowly tapered. Owing to persistent symptoms, one infusion with a tumour necrosis factor (TNF)-α inhibitor (infliximab) 5 mg $kg^{-1}$ was applied. Diarrhoea improved and nivolumab was restarted 1 month after cessation. However, in the following 3 months, new disseminated erythematous and ulcerated plaques appeared and the patient developed a painful massive swelling in the preauricular region. MRI showed a mass in the parotid lodge infiltrating the masseter muscle. Treatment was switched to total body irradiation. However, the patient's condition deteriorated rapidly and she died from sepsis 14 months after diagnosis.

Checkpoint inhibitors play an increasing role in the treatment of patients with solid and haematological malignancies. More recent studies evaluated the safety and efficacy of anti-PD-1 antibodies in patients with cutaneous T-cell lymphomas, including

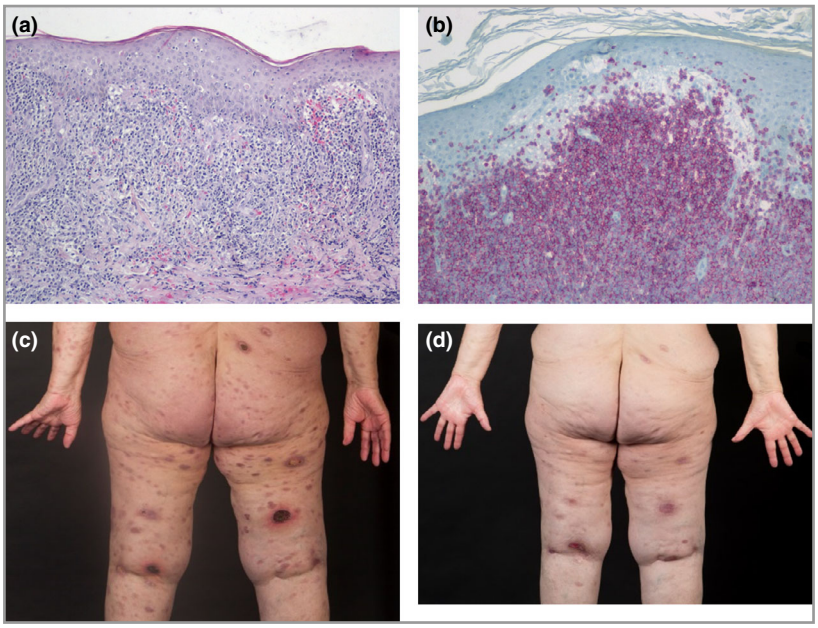


**Figure 1** (a) Intraepidermal and dermal multifocal infiltrates of atypical lymphocytes (haematoxylin and eosin staining; original magnification × 100). (b) Positive immunohistochemical staining for CD8 (original magnification × 100). (c) Clinical image before starting treatment with nivolumab and (d) after five infusions of nivolumab.

a phase Ib study for nivolumab that included 13 cases of mycosis fungoides and five cases of peripheral T-cell lymphoma. The objective response rate in that study was 15% among patients with mycosis fungoides and 40% among patients with peripheral T-cell lymphoma with no further specification of the subtype.[2] A phase II study of 24 patients with pretreated mycosis fungoides and Sézary syndrome showed an overall response rate of 38%.[3] To our knowledge, there are no descriptions of treatment of $CD8^+$ AECTCL with anti-PD-1 antibody. Reported treatment regimens in cases of $CD8^+$ AECTCL consist of polychemotherapies with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). However, results are disappointing, with limited success and often rapid recurrence.[4]

So far the most promising results were achieved with allogeneic hematopoietic stem cell transplantation with a possible curative option,[5,6] which was not possible in our patient owing to rapid progression after multiagent chemotherapy, age and comorbidity. Our patient initially responded surprisingly well to therapy with anti-PD-1 antibody. However, after a short duration of nearly complete remission she required immunosuppressive medication including TNF-α inhibitor in steroid-refractory immune-related diarrhoea. Subsequently, the disease recurred with rapid progression and she finally died, 14 months after diagnosis of $CD8^+$ AECTCL, due to sepsis. There is ongoing discussion of whether treatment with TNF-α inhibitors could induce progress of cutaneous lymphoma.[7] Also in our case, it is not excluded that disease progression was accelerated by anti-TNF-α treatment.

In conclusion, anti-PD-1 antibodies present a potential treatment option for $CD8^+$ AECTCL, an entity with otherwise few options.

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**[Correction added on 7 Jan 2020, after first online publication: F. Toussaint was designated as co-corresponding author].*

## References

1 Willemze R, Cerroni L, Kempf W *et al.* The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019; **133**:1703–14.

2 Lesokhin AM, Ansell SM, Armand P *et al.* Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol* 2016; **34**:2698–704.

3 Khodadoust MS, Rook AH, Porcu P *et al.* Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. *J Clin Oncol* 2020; **38**:20–8.

4 Nofal A, Abdel-Mawla MY, Assaf M, Salah E. Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. *J Am Acad Dermatol* 2012; **67**:748–59.

5 Plachouri KM, Weishaupt C, Metze D *et al.* Complete durable remission of a fulminant primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma after autologous and allogeneic hematopoietic stem cell transplantation. *JAAD Case Rep* 2017; **3**:196–9.

6 Liu V, Cutler CS, Young AZ. Case records of the Massachusetts General Hospital. Case 38–2007. A 44-year-old woman with generalized, painful, ulcerated skin lesions. *N Engl J Med* 2007; **357**: 2496–505.
7 Martinez-Escala ME, Posligua AL, Wickless H *et al*. Progression of undiagnosed cutaneous lymphoma after anti-tumor necrosis factor-alpha therapy. *J Am Acad Dermatol* 2018; **78**:1068–76.

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## Recurrent *MVD* mutation in European patients with disseminated porokeratosis

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Dear Editor, Porokeratosis comprises clinically and genetically heterogeneous disorders of keratinization. They manifest with marginate scaling lesions, histologically showing a column of parakeratotic keratinocytes, the cornoid lamella. Porokeratotic conditions were historically classified into several clinical forms based on the distribution and morphology of the lesions, for example disseminated porokeratoses, porokeratosis of Mibelli, giant porokeratosis, palmoplantar porokeratosis Mantoux and linear porokeratosis. Several clinical forms are associated with second-hit genetic changes in the presence of monoallelic germline mutations in genes encoding enzymes of the mevalonate pathway (*MVK*, *PMVK*, *MVD* and *FDPS*), suggesting therefore common pathogenetic mechanisms.[1–5] In addition, mutations in other genes, such as *SLC17A9*[6] and *SSH1*,[7] have been reported in disseminated porokeratosis.

The terminology making use of eponyms and descriptive terms is confusing and requires thorough revision based on recent molecular genetic data. The treatment of porokeratoses is challenging due to the modest therapeutic response to classical measures (e.g. keratolytics and retinoids) and to the multitude of lesions, which spread over large body areas. Pathogenetic-based topical treatment with statins that target the mevalonate pathway and cholesterol biosynthesis was recently shown to be effective in disseminated porokeratosis.[8]

Here we performed molecular genetic analysis of skin samples of eight patients with disseminated porokeratosis. All patients were white with skin phototype I or II. Three had a positive family history of porokeratosis, and the other cases

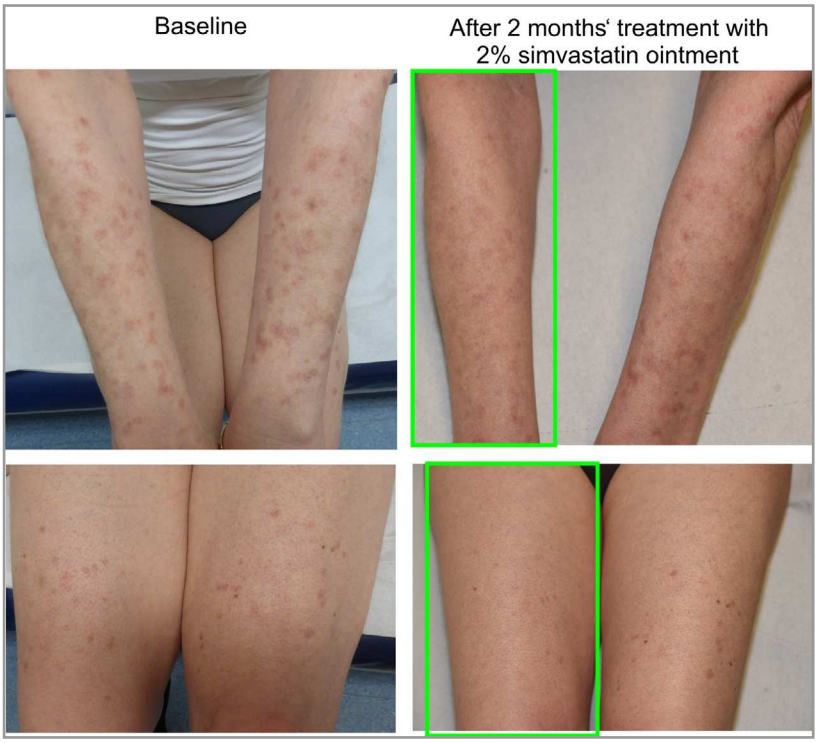


**Figure 1** Clinical manifestations before and after treatment with simvastatin ointment in patient 1. (a) Before treatment, the patient presented porokeratotic lesions on the arms and legs. (b) After 2 months of treatment of the right arm and leg (green frame) with an ointment containing simvastatin the lesions almost disappeared. She noticed the benefit only after the first 3 weeks of treatment. The left side of the body was treated with moisturizer.